The Globalization of Cooperative Groups

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ABSTRACT

The National Cancer Institute-supported adult cooperative oncology research groups (now officially Network groups) have a long-standing history of participating in international collaborations throughout the world. Most

frequently, the U.S. based cooperative groups work reciprocally with the Canadian national adult cancer clinical trial group, NCIC CTG (previously the National Cancer Institute of Canada Clinical Trials Group). Thus, Canada is the largest contributor to cooperative groups based in the U.S., and vice versa.

Although international collaborations have many benefits, they are most frequently utilized to enhance patient accrual to large phase III trials originating in the U.S. or Canada. Within the cooperative group setting, adequate attention has not been given to the study of cancers that are unique to countries outside the U.S. and Canada, such as those frequently associated with infections in Latin America, Asia and Africa. Global collaborations are limited by a number of barriers, some of which are unique to the countries involved, while others are related to financial support and to U.S. policies that restrict drug distribution outside the U.S. This manuscript serves to detail the cooperative group experience in international research and describe how international collaboration in cancer clinical trials is a promising and important area that requires greater consideration in the future.

INTRODUCTION

Cancer is one of the most common worldwide causes of morbidity and mortality. It is estimated that in 2012, there were 14.1 million adults diagnosed with cancer and 8.2 million deaths attributable to this disease. It is also estimated that the number of cancer cases will increase from 14.1 million in 2012 to 22 million in

the next two decades.¹ The most common cancers in adults are breast, prostate, lung and gastric cancers. From the standpoint of mortality, lung and gastric cancers are, respectively, the first and second most common causes of cancer death in the world.² Globally, more than 60% of the total number of new cases diagnosed annually occur in Africa, Asia and Central and South America. These regions account for 70% of the world's cancer deaths.¹ This is particularly important to the U.S. and other developed countries because of immigration from these regions and its subsequent effect on the makeup of their populations. For example, Hispanics are the largest minority in the U.S., comprising 16.3% of the total population in 2010, and having grown by 43% since 2000. At this rate, it is estimated that by 2050, one of every four Americans will be Hispanic.³ It is not fully known what the impacts of immigration will be on cancer epidemiology in the US, but it behooves the U.S. medical community to be prepared for change.

Cancer-related risk factors also vary geographically. Tobacco use is the most important cancer risk factor responsible for 20% of global cancer deaths and approximately 70% of global lung cancer deaths. Infections represent a risk factor that starkly differs among regions, and they are related to 8% of cancers in developed nations and up to 23% in countries under development. Cancer causing viral infections such as HBV/HCV and HPV are responsible for up to 20% of cancer deaths in low- and middle-income countries.² Cervical cancer, a

consequence of HPV along with lack of access to appropriate screening, is a leading cause of death in low-income countries.

With the increasing improvements in our understanding of the molecular biology of cancer and the subsequent development of improved methods of cancer prevention, detection and therapy, there is increasing interest in applying these methods to improve cancer control throughout the world. In the U.S., these efforts are led by the National Cancer Institute (NCI) through its Center of Global Health and other institutes at the National Institute of Health (NIH). Trimble et al. has described these efforts and those of other centers around the world, efforts that have led to improved standardization of cancer staging, increased awareness of the importance of securing patient's informed consent, better understanding of developing, applying, monitoring and publishing cancer clinical trials, as well as the limitations of applying these efforts due to economics, politics, regulatory, tissue procurement and distribution, drug distribution and other issues.⁴

Additionally, and in response to the increasing interest of U.S. Cooperative Groups in international trials participation, the NCI-CTEP is working collaboratively with both the Food and Drug Administration (FDA) and with the Office for Human Research Protections (OHRP) on the clarification of regulatory and logistical aspects regarding the entire clinical trials process, including design, implementation, monitoring, analysis and publication of trial results that include

NCI-sponsored Cancer Cooperative Groups

(http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/nci_clin_intl_guidelines.pdf).

As an extension of the interest of the US Government to improve the infrastructure of Europe after the Second World War, resources were provided for the establishment of the European Organization for Research and Treatment of Cancer (EORTC) in 1962. Subsequently, funding assistance was provided to the former National Cancer Institute of Canada Clinical Trials Group (now known as “NCIC Clinical Trials Group”) (NCIC CTG)) in 1997. All involved countries have significantly now contributed to the sustainability of these efforts.

The NCI-sponsored U.S., Network groups have extended their trial network to include many countries around the world. These efforts have been primarily focused on Canada, where a strong clinical research partnership has been developed with the NCI CTG. Other efforts principally involve Europe and Australia and, to a lesser extent, Asia and Latin America. This article provides an overview of international collaborations coordinated by the NCI-sponsored adult cooperative oncology research groups.

SEEKING INFORMATION ON GLOBALIZATION FROM ADULT COOPERATIVE GROUPS

The leadership of the NCTN was invited to participate in this review and asked to provide their experience on international collaborations, including information on countries, sites, investigators, and clinical trials and associated publications.

This article includes summary tables of the groups' involvement in international collaborations, although data on patient accrual and publications are available for only those groups providing this information. Overall activity is summarized in Table 1.

NCIC CTG EXPERIENCE

Overview and the NCIC CTG Perspective

Established in 1980, the NCIC CTG has 273 phase III ongoing or completed studies, as well as 197 Investigational New Drug trials, enrolling a total of over 75,000 patients. NCIC CTG has collaborated with sites in 41 countries, across 54 trials, with 26189 patients accrued. It is important to note the significance of the partnership with US cooperative groups and sites that contributed 18624 of the 26189 patients accrued through these collaborations. A summary of international participation is provided in Table 2.⁵⁻⁴⁹ Globalization of clinical trials is critical in moving the research agenda forward. Benefits of globalization include: a) facilitation of regulatory filings in multiple regions using a Common Technical Document (CTD); b) increased applicability of results to multiple regions; c) increased speed in time to activate, accrue, analyze and, ultimately, answer the

trial question; and, d) access to emerging information and new treatment options for patients in need. Given the benefits, continued effort is essential to overcome the economic, political, regulatory, contractual, and drug related challenges in the global clinical trials environment.

History of Collaboration

NCIC CTG has collaborated with international sites in the US and Europe since the early 1980's. This expanded to cooperative group collaborations in the early 1990's. Subsequently, NCIC CTG successfully applied for NCI/CTEP funding in 1997. This grant, renewed in 2003 and 2008, serves two main purposes: i) to develop, conduct and provide leadership of trials that engage the U.S. investigative community in a manner that meets U.S. scientific interests, regulatory standards and represents value from the perspective of expenditure of U.S. federal dollars; and, ii) to conduct in Canada trials led by U.S.-based groups, including the provision of operational and regulatory oversight that complies with U.S. and Canadian expectations and requirements. Important secondary purposes include contributions to scientific, operational, data management and regulatory advancements. More recently, the NCIC CTG became the Canadian Collaborating Partner of the National Clinical Trials Network (NCTN) with the aim to continue to enhance these relationships through the contributions of a highly organized Canadian network.

Models of Collaboration

NCIC CTG conducts these trials in several ways referred to as the Intergroup or International models. In the Intergroup Model, the lead cooperative group would organize the trial and communication strategy, oversee all central data management and cleaning, analyze the trial, and prepare the primary publication. The lead cooperative group would also act as sponsor with associated responsibilities in their own region. From there, other academic cooperative groups could join and an Intergroup Agreement with roles and responsibilities assigned would be executed. The other academic cooperative groups would act as local sponsor in their region, be responsible for site activation and data collection, as any issues that may arise. The intergroup model is typically found to be more cost effective and generally uses a risk-based approach (i.e., regulatory risk differentiation to systemically treat entities differently based on the regulator's assessment of the risks of the entity's non-compliance) to oversight and quality assurance processes. An example of the Intergroup Model is the MA32 study, *A Phase III Randomized Trial of Metformin versus Placebo on Recurrence and Survival in Early Stage Breast Cancer*, This trial was developed by NCIC CTG, activated 2010 JUN 25, and closed to accrual 2013 JAN 22. Including Canada, international centers and groups from Switzerland, the UK, and the US participated in the study. A total of 3649 patients were accrued with 33% coming

from Canada and 67% from the rest of the world with the majority through the US CTSU mechanism. The international partnerships facilitated timely activation and accrual.

In the International Model, the lead cooperative group would similarly enter into a contract with a pharmaceutical partner and from there lead organization/communication on the trial, oversee all central data management and cleaning, and ultimately analyze and publish/present the trial. The lead cooperative group would also act as sponsor with associated responsibilities in their own region. From there, company would act as local sponsor or this may be delegated to a Contract Research Organization (CRO). The international model is typically most resource and cost intensive and often used when new registration of an agent is planned.

A successful example of the International Model was the BR21 study, A *Randomized Placebo Controlled Study of OSI-774 (Tarceva) in Patients with Incurable Stage IIIB/IV Non-Small Cell Lung Cancer Who Have Failed Standard Therapy for Advanced or Metastatic Disease.*⁵ This trial was developed by NCIC CTG, was activated on 2001 AUG 14, the first patient was randomized 2001 NOV 01, and the trial completed accrual on 2003 JAN 31, just over 2 years after the trial was activated. Including Canada, 17 countries and 97 centers participated

around the world. A total of 731 patients were randomized with 25% of patients coming from Canada and 75% from the rest of the world. Benefits of this international effort included speed in time to activate, accrue, and ultimately answer the study question. This also facilitated filings as well as increased applicability of study results in multiple regions. This study would not have been possible without the partnership around the world.

NSABP EXPERIENCE

The list of international sites that have participated in current and past NSABP studies covers the period from 1971 to the present. It includes 41 different institutions or organizations. Some of the organizations are actually themselves research groups, such as the Irish Clinical Oncology research Group (ICORG), which participated as full members of the NSABP. Overall, these sites have entered more than 14,000 patients into NSABP's NCI-funded CTEP trials or about 13% of the total accrual. This number does not include the NSABP's primary prevention trials supported through the NCI's Division of Cancer Prevention. Historically, all NSABP trials have been made available to its international participants, except in cases where the supporting pharmaceutical company had distribution or formulation issues that precluded activating a trial in a given country. More recently, NCI drug distribution and regulatory issues have hampered international participation. Individual institutions could self-select not to open a specific trial at their discretion.

Canadian participation has been particularly key to the success of NSABP studies. The Canadian sites have been major participants in many NSABP trials, and their investigators have been active in the scientific and administrative committees of the NSABP, including the Board of Directors. Dr. Alexander Patterson, from the Tom Baker Cancer Center in Calgary, is the protocol chair for NSABP Protocol B-34, “Clodronate With or Without Chemotherapy and/or Hormonal Therapy in Treating Women With Stage I or Stage II Breast Cancer,” which was recently published in *Lancet Oncology*.⁵⁰ Dr. Richard Margoless, from the Jewish General Hospital in Montreal, is the protocol chair for NSABP B-35, “Anastrozole or Tamoxifen in Treating Postmenopausal Women With Ductal Carcinoma in Situ Who Are Undergoing Lumpectomy and Radiation Therapy.” The B-35 study has completed accrual with 3000 patients but has not yet reached final data collection date for primary outcome measures. A summary of international participation in NSABP trials is provided in Table 3.⁵⁰⁻¹⁰³

RTOG EXPERIENCE

The RTOG elected to globalize its activity in 2004. The first international site to be accepted was Tel Aviv Medical Center. Within a year, hospitals from South

Korea and Australia were also invited to join as affiliates. Currently, 29 centers participate from 14 countries and 5 continents.

The motivation for expanding towards an international catchment was both altruistic and pragmatic in nature. From an altruistic standpoint, enrollment of patients on RTOG protocols would result in improving the standard of care for patients enrolled onto clinical trials, with an anticipated concomitant “spillover effect” for those receiving standard therapy in a facility whose rigor of quality assurance was very likely upgraded in order to achieve endorsement during RTOG audits. On a pragmatic level, RTOG leadership understood that international expansion would accelerate trial execution by virtue of rapid enrollment and would also provide access to genetically diverse populations not necessarily residing in North America. Furthermore, it was hoped that new standards emerging from RTOG protocols would more rapidly penetrate clinical practice if a broad set of international centers were to participate.

An illustrative case of the success of the RTOG Intercontinental Committee is derived from RTOG 0525. In that trial, the largest study to date conducted for glioblastoma multiforme (GBM), a very rare but particularly malignant brain tumor, the leading accruing site was an Intercontinental group member (Tel Aviv Medical Center). Some historical background is needed to understand what led to this exemplary participation.

In Israel, where national health legislation has been available in some form since the founding of the state in 1948, a committee meets annually to revise the “basket” of goods and services that are provided to all citizens.¹⁰⁵ Unfortunately, these entitlements often lag behind the establishment of new standards of care. In 2005, a study appeared in the *New England Journal of Medicine*, which established a new treatment paradigm for GBM. Stupp and colleagues demonstrated that instead of treating with radiotherapy alone, the combination of radiotherapy and Temozolomide nearly doubled survival rates.¹⁰⁶ The drug, manufactured by Schering Plough, was priced at 40,000 shekels (approximately \$10,000 USD in 2005) per month and was to be taken for a full year. Temozolomide, however, was not added to the aforementioned “basket” until approximately two years after the publication of the GBM trial. Israeli citizens diagnosed with GBM who could not afford to pay \$120,000 annually for the drug had no recourse. Because many of the Israeli patients were savvy medical consumers, a creative solution emerged. Israelis obtained access to a clinical trial sponsored by the National Cancer Institute (i.e., RTOG 0525), which randomized patients with GBM to irradiation plus standard dose temozolomide versus irradiation plus dose-intensified temozolomide. In both the standard and experimental arms of the study, patients received the drug gratis from the NCI. Hence, Israel became the leading site accruing patients to this study, outpacing even highly regarded academic facilities in the U.S.

An evolving story of success is RTOG 1119 for brain metastases in the context of Her-2 positive breast cancer. This randomized phase II trial was initiated by an Intercontinental Committee member from Seoul National University Bundang Hospital. In contrast to the case study of RTOG 0525, which was partly driven by the lack of availability of the lead drug (Temozolomide) at one of the centers, RTOG 1119 has thrived because of the ability of four centers comprising the Korean Radiation Oncology Group (KROG) to obtain the experimental agent (i.e., Lapatanib). Trial 1119, which offers many opportunities for comparative genetic studies among participating populations, emerged from fruitful discussions at the Intercontinental Committee of RTOG with subsequent input from the Brain Tumor Committee and the Breast Cancer Committee, respectively.

Indeed, medical centers from outside the boundaries of North America convene at the semi-annual meeting of the RTOG in the context of the “Intercontinental Committee” which has a Chair and a Vice Chair, who by definition represent separate countries of origin. At the most recent meeting of the Intercontinental Committee, an informal survey was conducted to identify common difficulties experienced while participating in RTOG trials (at that time under the auspices of NRG Oncology). Minor concerns included time zone difference vis-à-vis RTOG headquarters in Philadelphia, which relegated most communication to email

correspondence without a “personal touch.” Of greater concern was pressure from international centers to retain tissue locally at the same time most RTOG protocols are mandating specimen submission to the group’s genetic data bank, expense of translating and validating supplementary tools (especially quality-of-life related surveys) at a time when ancillary studies (e.g., neurocognitive testing) are being sought. In addition, a consensus – if not a grievance – existed in relation to the mandatory \$10,000 entrance fee for RTOG site membership used at that time to cover administrative expenses, including auditing activities. Overall, however, the participating intercontinental centers expressed pride to be a part of the RTOG, which is exemplified by the continuous stream of applicants seeking to join the group. The membership fee for international site participation within the context of NRG Oncology has been discontinued.

RTOG international participation is summarized in Table 4.¹⁰⁷⁻¹²⁶

SWOG EXPERIENCE

Over the past four decades, SWOG has collaborated with 93 centers in 14 countries, including 66 sites in Canada. A total of 8925 patients were accrued to 48 studies, including solid tumors and hematologic malignancies. Leading accruing sites were Canada (4522), Puerto Rico (1463), Mexico (678) and Spain (499). These studies generated the publication of 35 primary results papers.

Included were the evaluation of imatinib mesylate in patients with gastrointestinal stromal tumors¹²⁷; the evaluation of intermittent vs. continuous androgen deprivation in patients with prostate cancer¹²⁸; effect of selenium and vitamin E on risk of prostate cancer^{129, 130}; and prospective randomized clinical trial of three antibiotic regimens for the treatment of *Helicobacter pylori* infection in Latin America.^{131,132} International collaboration activity is summarized in Table 5.¹²⁷⁻¹⁶¹

A focused effort was made recently to study disease processes that were far more common in other countries than in the U.S., resulting in a prospective randomized clinical trial of three antibiotics regimen for the treatment of infection by *Helicobacter pylori* in seven sites, six countries, of Latin America.^{131,132} More than 1463 patients were accrued by the study sites. The investigators were highly capable and cooperative, and study requirements were met or exceeded. The study was principally supported by a grant from the Bill and Melinda Gates Foundation. Many lessons were learned with the implementation and conduct of this trial, including the different requirements and timetables of each country towards providing Institutional Review Board (IRB) approval. Several sites would not permit specimens to be collected and stored long term for future, unspecified use. The procurement and delivery of the urea breath tests (UBT) machine from Europe to each site, overcoming each country's customs authority,

and the reliable functioning of such machines offered challenges that needed great attention by the central coordinating center in the U.S. All study forms needed to be translated into Spanish; appropriate training of technical personnel was done on site; multiple queries were issued when data entry questions developed; weekly meetings of all investigators with the central coordinating center were conducted via telephone conferencing; and the central coordinating team conducted audit visits to each site twice a year.

Over the course of this trial, SWOG planned for regulatory delays, customs, drug distribution and specimen shipment. Chile experienced a devastating earthquake at the height of accrual. Nicaragua, Mexico and Costa Rica suffered the worst rainstorms in recent years knocking out power, washing away roads and creating food shortages. Honduras experienced a coup, and Colombia was in the middle of political elections that sporadically impacted trial operations. Despite the obstacles encountered along the way, the *Helicobacter pylori* trial was a success.^{131,132} Even with regulatory and customs delays, it reached accrual goals through the efforts of staff committed to the success of the trial. We encountered no significant problems with internet connectivity. Sites administered a total of 4,612 urea breath tests, and adverse events across all treatments were minimal. Most important of all, Latin American medical professionals can now confidently recommend the 14-day antibiotic regimen as the best regimen to eradicate

Helicobacter pylori in their patient populations, and we know that such trials can be successfully conducted in Latin America.

THE ALLIANCE EXPERIENCE:

The Alliance for Clinical Trials in Oncology was created as a merger between 3 “legacy” groups: ACOSOG, CALGB, and NCCTG. The 3 legacy groups all had a strong history of international sites and collaborations. Between the groups, there have been numerous collaborators, involving 2 countries in Australia, 10 in Asia, 2 in North America, 3 in South America and 21 in Europe, with a total international accrual of 10,105 since 1966. The summary of these experiences is detailed in Table 6.⁽¹⁶²⁻²¹²⁾

There are 2 trials that highlight work that began in the legacy groups and is being completed by the Alliance. The first is a trial, N063D, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial. ALTTO was a co-developed trial between the legacy NCCTG and the Breast International Group (BIG), with funding from the NCI and Glaxo Smith Kline. The trial was an excellent example of academic collaboration between the NCI and the international oncology institutions, with pharmaceutical partnership. All study forms were developed with input from all partners. The trial structure involved 2 co-PIs (one from each academic group), an executive committee that included a

statistician from each group and several global collaborators, and a steering committee of approximately 50 members. Added to almost daily global interactions via internet, there were monthly operations meetings during the 4 years of accrual, then less frequently afterwards.

The study helped identify barriers to trial activation in different countries, identified discordance problems with HER2 as a biomarker - which led to educational initiatives to improve validity of testing. All of this resulted in improved access to anti-HER2 therapies for women in more than 40 countries. The biospecimens collected will be used to conduct correlative studies for treatment efficacy and toxicity overall, and also to address potential differences based on country.

The Alliance also has worked on the completion of accrual and the analysis of data for CALGB 10603, “A Phase III randomized double blind study of induction (daunorubicin/ cytarabine) and consolidation (high-dose cytarabine) chemotherapy and midostaurin or placebo in newly diagnosed patients < 60 years of age with FLT3 mutated acute myeloid leukemia”, also known as the RATIFY trial. This was a complex, biomarker driven trial, involving collaborators from multiple countries or organizations (EORTC ; GIMEMA; German Austrian AML study group; OSHO; SAL; PETHEMA; CETLAM; Brazil; Hungary; Australia; France; Czech Republic; UK; Slovakia; Israel; Argentina; Mexico), with Richard

Stone, M.D., as the U.S. study chair. Again, there was presence of an industry collaborator in Novartis. The study accrued rapidly, with over 2400 AML patients pre-screened and over 700 patients enrolled in 3.5 years. Dissemination of biomarker results was very rapid, with US time of 26 hours, thus facilitating site participation. Operationally, while it was complex to organize, the trial ran well and was very successful, as evidenced by the rapid enrollment.^{202,203} Linda Bressler, Pharm. D., should be credited for her diligence and dedication to the trial, and her time invested in operations.

There are several recent collaborations described below that have identified hurdles which exist for international collaborations as a whole, and the barriers found are representative of international cooperative group studies of the present and future:

- Two collaborations are being investigated with the EORTC, for testicular cancer and for salivary cancer
- Collaboration with Switzerland (SAKK) and with Hospital de Gastroenterología Dr. Carlos Bonorino Udaondo, Buenos Aires, Argentina, has been finalized for study N1048, “A Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision.”

- Collaboration is ongoing with several Canadian member sites, Princess Margaret Cancer Center, Toronto, ON, Canada; London Regional Cancer Center, London, ON, Canada; Allan Blair Cancer Centre, Regina, SK, Canada on multiple trials.

- All of these studies require utmost attention to detail with regard to initial feasibility, then the appropriate delineation of responsibilities for the Alliance and the counterpart abroad, including the following issues:
 - scientific agreement on the study and its design between the U.S., non-U.S. group, and the NCI
 - linguistic translation of protocol, study forms and consent form
 - development of group-specific appendix
 - handling of protocol amendments
 - obtaining and shipping biologic samples under biobanking agreement when needed
 - costs of shipping specimens and banking; maintaining specimen conditions with international shipment
 - coordinating techniques between central labs in separate nations to ensure uniformity
 - drug supply, distribution and import/export arrangements

- studies of quality of life with instruments that have been approved among collaborating partners and language barriers therein
 - developing an agreement/ that is approved by both parties and the NCI
 - harmonizing registration/randomization in 1 system
 - meeting clinical NCI reporting requirements with a non-U.S. database
 - rostering of international members
 - coordinating separate IT systems
 - simultaneous collaboration with pharmaceutical companies
 - time zone differences especially in answering urgent queries or dealing with safety
 - capacity of a study site to meet accrual expectations for membership
 - study site burden in utilizing a novel electronic case record form
- International collaborations further include daunting regulatory considerations, as the regulations need to be met for both sides. Some of the major regulatory hurdles that need to be resolved are the following:

- differing guidelines and regulations for safety reporting and pharmacovigilance with resultant needs for double reporting for sites and burdens on the cooperative group
- meeting drug labeling requirements and other regulatory considerations surrounding drug
- meeting and harmonizing the data protection directives and privacy laws which differ between countries
- differences in regulations for record retention and their subsequent harmonization
- coordination of audit techniques and their approvals;
- periodic audit of member sites with resultant financial cost and resource loss for audits outside the US
- obtaining human subject protection and state department clearances
- harmonizing of regulations for IRB/ethics committees
- paperwork burden and additional training for sites and investigators
- study specific certifications such as radiation safety and therapy certifications.

DISCUSSION

NCTN groups have a long-standing history of collaboration with international cancer units around the world. The most important incentive for these collaborations appears to be the desire to improve patient accrual of large phase III trials in the U.S. and Canada. Many international sites likewise benefit by the experience of working with well-organized and experienced clinical trials organizations that facilitate their access to newer and often expensive cancer treatments provided by the treatment protocols. These interactions are usually viewed very positively by all of the parties involved.

Cooperative groups in the U.S. have reached out to many countries around the world, mainly Canada, Western Europe, Australia and Latin America. Canada, by far, is the most active participant accruing patients onto U.S.-based clinical trials. The same reciprocal phenomenon is observed in Canada, since the U.S. is responsible for the largest number of patients accrued onto NCIC CTG-based protocols. Hence, a close clinical trials collaboration has thus evolved between the two countries.

NCIC CTG competes for funding from the U.S. government, as do the other cooperative groups, so the benefit sought by the funding agency in terms of larger accrual to clinical trials is achieved. These and other international collaborations

have resulted in important contributions to the cancer literature. Similar success has been achieved in Europe with its own European Organization for Research and Treatment of Cancer (EORTC) based on strong collaboration among European nations although this collaboration has occasionally included the U.S. and Canada.

It is important to realize that the support provided by the U.S. government to Europe, including the formation of the EORTC, was a success. Similarly, the support of the U.S. to Canada for the NCIC CTG to expand collaborations with U.S. cooperative groups has successfully enriched trial opportunities for patients and improved trial recruitment in both countries. Unfortunately, other parts of the world with important cancer issues, such as infection-related cancers, lag in support by their own countries and the U.S. government. Included are Africa, parts of Asia and Latin America - the latter, our neighbors to the south, with over 700 million inhabitants. The continuing immigration of large numbers of Hispanics to this country and the rapid growth of Hispanics in the U.S. make the need for cancer research efforts in Latin America even more critical.

The international collaboration of U.S.-funded cooperative groups has until now, not focused on the study of genomics of common cancers in distant parts of the world. Such study could produce meaningful results for cancer control and

treatment in those areas. Also, there has been a notable lack of clinical trials designed to prevent, treat and study infection-related cancers. In general and genomically cancers of the stomach, cervix and liver are due to *Helicobacter pylori*, HPV and HBV/HCV, respectively and require attention of global collaborative partnerships. They are common in countries under development and often represent the most common causes of cancer incidence and mortality in some areas of Latin America, Asia and Africa. In this regard, the efforts of SWOG in developing treatment protocols for *H. pylori* infection in Latin America have been highly successful.^{131,132} The NCI has also started a pilot clinical genomic protocol of 1000 breast cancer patients in several countries of Latin America (<http://www.cancer.gov/aboutnci/organization/global-health/research-programs-initiatives/us-la-crn>) that is being conducted by the Latin America Research Network (US-LA CRN). These initial steps are important and, hopefully, will be expanded in the future.

The conduct of international cancer clinical trials still faces a number of challenges. Aside from the need to translate clinical trial protocols into another language(s), there is the necessity for adequate contracting to assure that responsibilities are carefully elucidated, and the need to attend to regulatory constraints unique to the country and often difficult to resolve, particularly with respect to biospecimen collection and release. Drug supply and distribution to

international sites is frequently difficult and not facilitated by current U.S. policies. All of these factors may adversely affect the conduct of the clinical trial abroad. In addition, close monitoring of such trials must be performed to assure patient safety. Last but not least, appropriate funding of international trials must be scrutinized as the costs of conducting trials abroad are, at times, more expensive than in the US. In spite of these deterrents, international collaborations are of benefit to all involved and, most importantly, to participating, current, and future cancer patients.

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Table 1. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS*				
COOP. GROUP	NUMBER COUNTRIES	NUMBER PARTICIPATING INSTITUTIONS	NUMBER OF STUDIES	OVERALL ACCRUAL
Alliance	19	243	402	10,105
NCIC-CTG	41	2485	54	26,189
NSABP	6	41	56	14,559
RTOG	9	47	83	4,040
SWOG	14	93	48	8,925
*Time periods: Alliance and legacy (1966-present); NCIC-CTG (1980-2014); NSABP (1971-2014); RTOG (2005-2014); SWOG (1970-present)				

Table 2

Table 2. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS: NCIC CTG (1980-2014)				
CONTINENT/ SUBCONTINENT*	NUMBER COUNTRIES/ SITES	STUDIES	OVERALL ACCRUAL	PUBLICATIONS (refs)**
Africa	1/8	BR2, BR21, MA19, OV12	97	(5-49)
America (North)	1/1696	BR10, BR18, BR19, BR2, BR21, BR26, BR8, CO10, CO21, CX3, EN5, HD6, I125, I152, I165, I202, I48, LY12, MA14, MA17, MA17R, MA20, MA21, MA27, MA31, MA32, MAP1, MAP2, MAP3, MY10, MY7, OV21, PA1, PA3, PR11, PR3, PR7, SC11, SC20	18,624	
America (Central & South)	5/39	BR21, BR24, BR26, BR29, MA31, PA3	419	
Asia	8/60	BR21, BR24, BR26, MA31, CE6, CO23, , CX5, PA3	484	
Australia	2/163	BR21, BR24, BR26, BR29, CE6, CO17, CO20, CO21, CO23, EN5, HD4, I7, LY12, MA19, MA20, MA31, PA3, SC20	1,587	
Europe	22/506	BR12, BR18, BR21, BR24, BR26, CE6, CX5, HD6, I106, I106B, I126, I138, LY12, MA17, MA19, , MA27, MA31, MA32, MAP3, OV9, OV12, OV16, OV21, PA3, PR7, PR11, SC20	4,870	
Middle East	2/13	BR21, CX2, MA31, OV12, PA3	108	
	41/2485	54	26,189	
*North America: U.S.; Central & South American: Argentina, Brazil, Chile, Mexico, Peru; Asia: Hong Kong, India; Japan, Philippines, Singapore, S. Korea, Taiwan, Thailand); Europe: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain Sweden, Switzerland, Ukraine, United Kingdom; Middle East: Israel and Saudi Arabia				
**Source: NCIC CTG				

Table 3

Table 3. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS: NSABP (1971-present)				
COUNTRY	NUMBER SITES	STUDIES	OVERALL ACCRUAL	PUBLICATIONS (refs)*
Australia/ New Zealand	2	B-06, C-06, C-07	179	(50-103)
Canada	36	B-04, B-05, B-06, B-07, B-08, B-09, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-42, B-43, B-47, B-51, B-52, B-59, C-01, C-02, C-03, C-04, C-05, C-06, C-07, R-01, R-02, R-03, R-04, P-1, P-2	13,949	
France	1	B-07, B-10	47	
Ireland	1	C-08, B-38, B-39, B-42, -B47	368	
Korea	1	B-43	16	
6	41	56	14,559	
*Source: NSAPB, Clinical Trials.gov				

Table 4

Table 4. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS: RTOG (2005-2014)				
COUNTRY	NUMBER SITES	STUDIES	OVERALL ACCRUAL	PUBLICATIONS (refs)*
Australia	1	R0214, R0521	16	(107-126)
Hong Kong	2	R0534, R0615, R0724, R0920, R0921, R1005, R1203	23	
Israel	3	R98-04, R9813, R0227, R0320, R0413, R0433, R0525, R0534, R0539, R0611, R0625, R0631, R0825, R0848, R0913, R0924, R0937, R1005	242	
Japan	1	R1005	5	
Rep Korea	7	R0214, R0235, R0724, R1005, R1119	100	
Saudi Arabia	1	R0417, R0627, R0920, R1008, R1174	30	
Singapore	2	R1005, R1203	20	
Switzerland	1	R0415, R0433, R1005	38	
Canada	29	R9804, R9813, R0022, R0116, R0117, R0123, R0126, R0129, R0212, R0213, R0214, R0215, R0225, R0227, R0232, R0233, R0234, R0236, R0239, R0244, R0247, R0315, R0320, R0321, R0324, R0330, R0412, R0415, R0417, R0418, R0420, R0424, R0436, R0438, R0514, R0515, R0518, R0521, R0522, R0524, R0525, R0526, R0529, R0534, R0539, R0611, R0614, R0615, R0617, R0618, R0627, R0630, R0631, R0712, R0724, R0813, R0815, R0822, R0825, R0831, R0848, R0913, R0915, R0921, R0920, R0924, R0925, R0926, R0933, R0937, R0938, R1005, R1008, R1016, R1106, R1112, R1115, R1119, R1203	3,566	
9	47	83	4,040	
*References provided by RTOG Note: Sites in Canada have been participating since 1987. This table includes 2005-2014 information only.				

Table 5

Table 5. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS: SWOG (1970-present)					
COUNTRY	NUMBER SITES	STUDIES	OVERALL ACCRUAL	PUBLICATIONS (refs)*	
Canada	66	S0000, S0033, S0106, S0205, S0772/S0773, S0774/ S0775, S0221, S0226,S1117, S1203, S7204, S7827, S7936, S8110, S8710, S9013, S9114, S9304, S9321, S9346, S9436, S9462, S9463, S9704, S9900	4,522	(127-161)	
Chile	1	S0701	277		
Columbia	2	S1007, S0701	259		
Costa Rica	1	S0701	276		
Egypt	1	S7436, S7519, S7521, S7524, S7610, S7613, S7632, S7727, S7765, S7814, S7817, S7820, S7965	268		
Honduras	1	S0701	259		
Korea	2	S1007, S9008	98		
Mexico	4	S1007, S0819, S0702, S0701, S7315	678		
Nicaragua	1	S0701	241		
Peru	2	S7416, S7426	40		
Puerto Rico	9	S0774/S0775, S0000	1,463		
Saudi Arabia	1	S0230, S0777, S0702	32		
Spain	1	S1007	499		
Sweden	1	S0106	13		
14	93	48	8,925		
*References provided by SWOG					

Table 6

Table 6. INTERNATIONAL PARTICIPATION IN NCI COOPERATIVE GROUP CLINICAL TRIALS: Alliance for Clinical Trials in Oncology and Legacy Groups (1966-present)*				
COUNTRIES	NUMBER SITES	STUDIES	OVERALL ACCRUAL	PUBLICATIONS (refs)†
Australia	3	CALGB-10603, CALGB-140503, CALGB-580602, Z0010, Z0011, Z0030	103	(162-212)
Austria	1	N0577	1	
Belgium	1	N0577	2	
Canada	76	ACOSOG = 17 studies from 1990 to present CALGB = 215 studies from 1966 to present NCCTG = 147 studies from 1979 to present Alliance = 1 study (A021202) from 2013 to present	7,513	
Denmark	1	CALGB = 60 studies from 1966 to 1992	771	
France	4	N0147, N0577	6	
Germany	73	CALGB-10603	328	
Great Britain (UK)	20	C9581, N0147	96	
Hungary	1	CALGB-10603	2	
Ireland	3	Z1031, Z0010, Z0011, Z1031	117	
Israel	1	C9710	15	
Italy	24	CALGB-10603	105	
Mexico	1	N0021, N0032, N0424, N0691	23	
Netherlands	18	C9581, N0577	51	
New Zealand	1	N9431	159	
Peru	1	C150106, C70103, C9710, CALGB-10403, CALGB-49907, N9831	94	
South Africa	2	CALGB-40101, N0691, N0832, N9741, N9831, N9841	94	
Spain	8	CALGB-10603	22	
Switzerland	4	CALGB = 34 studies from 1966 to 1981	617	
19	243	402	10,105	
*Legacy Groups: American College of Surgeons Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group; †References provided by Alliance for Clinical Trials in Oncology				